

Effect of Leukocyte- and Platelet-Rich Fibrin in Postoperative Recovery Following Impacted Mandibular Third Molar Surgery: A Split Mouth Study

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Abstract: *Objective:* The surgeries for extraction of impacted lower third molars are more associated with complications such as pain and postoperative edema. The purpose of the present study was to evaluate the impact of the use of Leukocyte- and Platelet-Rich Fibrin (L-PRF) on pain and edema after extraction of impacted mandibular third molars.

Material and Methods: A cross-sectional split-mouth study was conducted with 15 volunteer patients who had both impacted mandibular third molars with indication for extraction. The removal surgery was performed one side at a time, with an interval of 14 days. One side received L-PRF while the other did not. Patients were evaluated on the 2nd and 7th postoperative days for mouth opening, pain and edema.

Results: In total, data from 14 patients (4 men and 10 women), with a mean age of 21.83 ± 2.8 years were evaluated. There was no statistically significant difference regarding mouth opening, pain and edema on the 7th postoperative day. On the second postoperative day, greater edema was observed in the control group with a statistically significant difference ($p = 0.01$).

Conclusions: Under controlled conditions, the L-PRF does not appear to alter postoperative recovery after extraction of the lower third molars in terms of pain, edema and the ability to open the mouth. Despite the statistically significant difference in edema on the second day, the means were very close and were not clinically relevant.

Keywords: Leukocyte- and Platelet-Rich Fibrin, Post-surgical Pain; Postoperative Complication; Tooth Extractions; Wisdom Tooth.

CLINICAL RELEVANCE

The purpose of this study is to evaluate the effects of L-PRF on postoperative recovery from surgery to remove the impacted mandibular third molars. This study represents a current trend regarding the use of L-PRF in oral surgery procedures. This technology has extensively used in dental implants and bone grafts surgeries. However, has few studies reporting the use of L-PRF in third molar removal surgery. Besides that, there is some controversial regarding centrifugation protocol and clinical outcomes. This study didn't find evident clinical benefits with the use of L-PRF in impacted lower thirs molar surgeries. Maybe, in case of most traumatical surgeries it can be used to reduce the edema and pain. But most patients did not see benefits from this therapy and they will not be willing to go through this again. It is important to be aware of the

aspects of the technique for obtaining the L-PRF, following the protocols established in the literature so that the best results are obtained in maintaining the viability of the cells present in the buffy coat aggregate.

INTRODUCTION

The inflammatory response related to the extraction of the impacted third molars shows an exacerbation when related to other regions. What can be associated with the surgical maneuvers necessary to remove the dental element include flaps, odontomy and osteotomy [1]. In addition, the inadequate execution of the operative technique must also be recognized as an exacerbating factor of the inflammatory reaction [2].

The applications and benefits of autologous Leukocyte- and Platelet-Rich Fibrin (L-PRF) in the healing of surgical wounds are well documented in the literature. As a result, several studies point out its anti-inflammatory and antibacterial properties, in addition to its ability to release growth factors, being then able to

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accelerate the local healing process of tissues and reduce pain in the postoperative period [3-7].

Several researches were carried out with the objective of determining the role of PRF in healing. Several growth factors found in platelets can provide stimuli to cells present in soft tissues. PRF is a second generation platelet aggregate, obtained by means of an inexpensive technique and facilitated by easy-to-handle instruments which dispenses with the addition of bovine thrombin, among other coagulants [3].

In 2009 the name L-PRF was introduced, based on the architecture and composition of the aggregate, which presents a thicker fibrin network due to the set of multiple fibers, thus making the matrix more resistant, in addition to the presence of leukocytes that are fundamental in the healing process of tissues [4].

The use of L-PRF in the post-extraction alveoli seems to accelerate healing and reduce postoperative pain and edema [6]. This is because it acts to repair and regulate the immune response due to the various cells and immunomodulators present in the fibrin clot [3]. In addition, recent studies demonstrate the ability of L-PRF to release growth factors from alpha granules released by platelets. In an *in vitro* study, the presence of TGF- β 1, PDGF, VEGF, FGF-2 and BMP-2 was demonstrated. TGF- β 1 acts by regulating several cellular functions, being desirable in oral wound healing sites where it stimulates osteoblasts and fibroblasts to proliferate. PDGF plays a role in the production of blood vessels (angiogenesis) and regulates the proliferation of stem cells that can differentiate into fibroblasts and osteoblasts. VEGF is a growth factor that stimulates blood vessel formation. FGF-2 is involved in angiogenesis, wound healing, and stimulates the proliferation and differentiation of pre-osteoblasts and fibroblasts. BMP-2 acts by stimulating the proliferation and differentiation of pre-osteoblasts and fibroblasts. That study demonstrated the presence of these proteins at 0, 7, and 14 after obtaining PRF, suggesting that they may help in accelerating and modulating wound repair [8].

However, the clinical relevance of L-PRF for the postoperative outcome is still controversial in the literature [4,5]. Thus, the present study aimed to evaluate the effects of PRF on postoperative recovery from surgery to remove the impacted mandibular third molars.

MATERIALS AND METHODS

A cross-sectional split mouth-type clinical study was carried out at the Dental Clinic of the Euro-American University Center (**Brasilia, Federal District, Brazil**) from August to November 2020. 15 healthy patients, aged between 18 and 30 years, with no history of systemic diseases (**hearth disease, diabetes, liver or kidney disease, metal disorder**) or use of medications in the last 30 days were included, which presented the two lower third molars in a similar position and classification by Pell & Gregory (1933) [9]. Patients with signs and symptoms of pericoronaritis, lactating patients, pregnant women, or those using systemic medications were excluded. This study was approved (**CAAE: 30575220.9.0000.5056**) by the ethics committee of the UNIEURO university center (**Brasília, Federal District, Brazil**) and all the patients signed de the informed consent. The sample size of interest was established based on the purpose of the study and the type of outcome. This study followed similar articles with the same study design. The split-mouth design removes a lot of inter-individual variability from the estimates of the treatment effect.

Surgical Procedures

All patients underwent surgery for extraction of the lower third molars in two sessions separated by a period of 14 days. The surgeries were performed by researchers with expertise in the area (DRG and MVS). Patients received preoperative medications: Amoxicillin 1g and dexamethasone 8 mg, orally, one hour before the procedure, **this is a protocol for the surgeries in the University Center**. The surgeries were performed under local anesthesia using 2% lidocaine and epinephrine 1:100,000, not exceeding 3 ml per procedure. The lower alveolar nerve and buccal nerve block techniques were used. **Beside the different position** all cases were performed with surgical access using an envelope-type flap with an intrasulcular linear incision involving the first and second mandibular molars and a linear incision with a 1 cm extension towards the mandible branch. Vestibular-distal ostectomy and odontosection were performed, when necessary, with a high-speed pen and number 702 HL stem-conical cutters under irrigation with sterile saline. After tooth removal and the pericorony cap, the alveolus was regularized with a bone file and the region was irrigated with 0.9% saline. For the third molars in the control test group (Figure 1-A),; 04 L-PRF plugs were placed and later suture with 4-0 nylon thread. For the third molars in the control group, (Figure 1-B) a

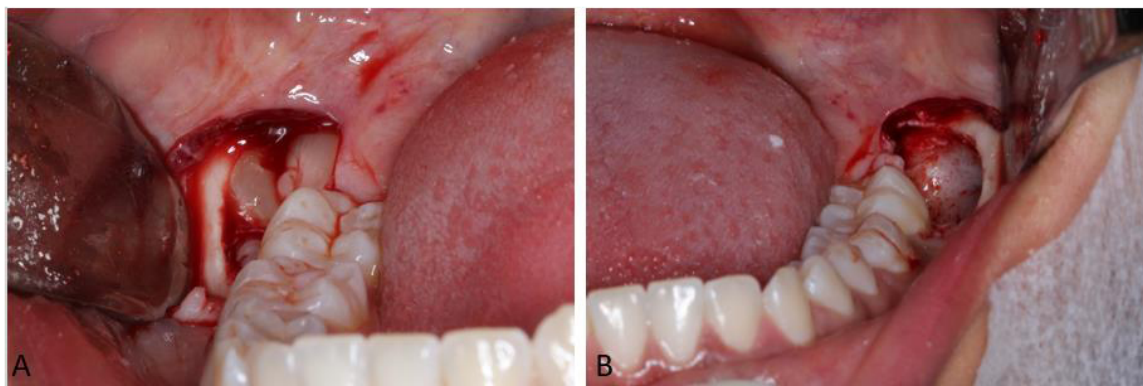


Figure 1: A, B: Transoperative image of an alveolus with (A) and without (B) L-PRF plugs.

sufficient number of simple interrupted suture was performed at this time with 4-0 nylon thread.

Patients received postoperative guidelines and were prescribed 100mg nimesulide (one tablet every 12 hours for the first three days) and 500mg Dipyron Sodium (one tablet every six hours on the first day). The average surgical time (from anesthesia to suture) was 12 minutes with no procedure exceeding 20 minutes. The first surgery could be with or without L-PRF, and the choice was made at random.

Obtaining the Fibrin Plug

Venous puncture was performed in the cephalic or basil vein in each patient for the collection of four 10ml tubes (Vacutainer®, BD Medical, New Jersey, USA) with clot activator. Immediately after blood collection, centrifugation was performed with the Kasvi PRP / PRF® centrifuge (Kasvi, São José dos Pinhais, Paraná, Brazil), at 1900 RPM for 12 minutes. The calculation of the revolutions per minute was carried out in order to reach the centrifugal force of 200g. After centrifuging, the fibrin plugs were removed from the tubes and

placed in the cases to be compressed and made into a membrane so that soon after the excision of the tooth, they were inserted into the empty alveolus.

Pre and Postoperative Evaluation

Patients were evaluated for mouth opening, edema and pain on the **preoperative moment**, second and seventh day after extraction. The measurement of mouth opening was performed using a caliper. The patient was asked to perform the maximum mouth opening and the pachymeter tips were positioned in the incisal of the upper and lower central incisors (Figure 2-A).

For the evaluation of edema, a transparent flexible ruler was used, adapted to the patients' faces between the tragus points and the labial commissure (Figure 2-B). To avoid conflicts in measurements, the same researcher carried out all the evaluations.

Pain was assessed using the visual analog scale (VAS). To use the VAS, the researcher asked the patients to indicate their degree of pain at the moment,

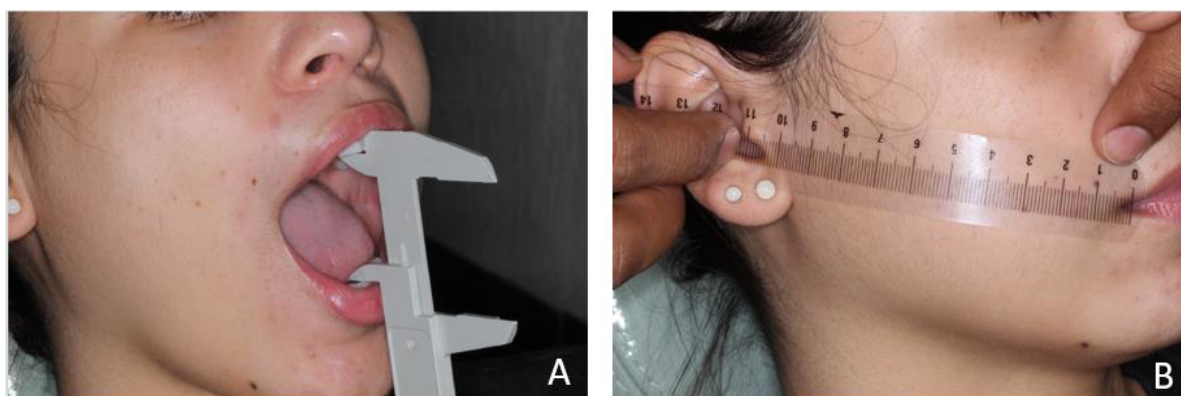


Figure 2: A, B: A caliper was placed on the upper and lower incisors to measure the maximum mouth opening (A).

A transparent flexible ruler was used for the evaluation of swelling of face, it was adapted to the patients' faces between the tragus and the labial commissure (B).

with 0 meaning total absence of pain and 10 the maximum pain level.

At the end of the study, patients' perception of venipuncture was assessed, so two questions were asked, which should be answered only with "yes" or "no". The questions were: "Do you think that recovery after surgery to remove the third molar on the side where the blood was collected was better?" and "Would you do the blood collection again for another surgical procedure?"

Statistical Analysis

Descriptive and comparative analyses was performed using the computer program SPSS® 18.0 (IBM) for Windows. Due to the size and distribution of the sample, a Wilcoxon test was performed for paired

samples, the results were considered statistically significant for values of $p < 0.05$.

RESULTS

In the present study, 15 patients were included, however, one patient abandoned the second stage (**didn't do the second surgery**) of the research and was excluded. Of the 14 patients, most were women ($n = 10$), the age of the participants ranged from 18 to 29 years, with a mean of 21.93 ± 2.81 years **and didn't have any adverse effects or complications**. Table 1 presents the demographic data and the position of the extracted teeth according to the classification of Pell and Gregory (1933) [9].

Table 2 presents the descriptive data of the measures of mouth opening and pain in the

Table 1: Demographic and Classification Characteristics According to PELL and Gregory of Mandibular Third Molars Extracted/ Extracted Teeth

Patient	Gender	Age	Control Group	Extracted Tooth	PRF	Extracted Tooth
1	F	23	Class II, position A	38	Class II, position A	48
2	M	22	Class I, position B	48	Class I, position B	38
3	F	18	Class II, position A	38	Class II, position A	48
4	F	20	Class III, position C	38	Class III, position C	48
5	M	21	Class II, position A	48	Class II, position B	38
6	F	29	Class II, position A	48	Class II, position A	38
7	F	25	Class I, position A	48	Class I, position A	38
8	F	19	Class II, position B	48	Class II, position B	38
9	F	19	Class I, position A	48	Class II, position B	38
10	M	24	Class II, position B	48	Class II, position B	38
11	F	24	Class II, position C	38	Class II, position C	48
12	F	22	Class II, position B	38	Class II, position B	48
13	M	21	Class II, position B	48	Class I, position A	38
14	F	21	Class II, position B	48	Class II, position B	38

Table 2: Assessment of Maximum Mouth Opening and Pain on the Second and Seventh Postoperative Days of Extraction Surgery of the Included Mandibular Third Molars

	Group	Mean	Standard Deviation	p*
Maximum mouth opening on the 2nd postoperative day	Control	33.93	12.406	0.60
	PRF	33.29	12.356	
Maximum mouth opening on the 7th postoperative day	Control	43.00	9.568	0.67
	PRF	43.21	9.593	
Pain according to the VAS on the 2nd postoperative day	Control	4.00	2.801	0.09
	PRF	2.14	1.994	
Pain according to the VAS on the 7th postoperative day	Control	0.57	1.222	0.10
	PRF	0.00	.000	

*Wilcoxon test.

Table 3: Evaluation of Edema on the Second and Seventh Postoperative Day of Extraction Surgery of the Included mandibular third Molars

Edema Measure	Groups	Mean	Standard Deviation	p*
Difference in the distance between the swallow and the two-day preoperative and postoperative labial commissure	Control	4.0	2.57	0.01
	PRF	3.64	5.30	
Difference in the distance between the swallow and the seven-day preoperative and postoperative labial commissure	Control	4.57	4.30	0.07
	PRF	2.14	4.45	

*Wilcoxon test.

postoperative period of two and seven days. There were no statistically significant differences between groups. Table 3 shows the measurements of postoperative edema. Greater edema was observed on the second postoperative day in the control group with a statistically significant difference ($p = 0.01$).

Regarding the patients' perception of the venipuncture procedure, most reported that the result on the side that received L-PRF had a better recovery and that they would perform the venipuncture again ($n = 8$). While for six patients the side that received L-PRF had a worse recovery and everyone in this group would not have the venipuncture procedure again.

DISCUSSION

Surgeons and patients seek post-operative recovery without impairing their functions, with minimal pain and swelling. Several therapies have been used in order to achieve the expected results, and the L-PRF has biological and scientific bases for its use after removal of the lower third molar [3]. However, clinically this result was not evident in the present study in which no differences were observed in relation to maximum mouth opening and postoperative pain. These findings corroborate the results of similar studies [10-12].

Studies show the importance of the centrifugation protocol for maintaining the biological properties of L-PRF [5]. We note a diversity of centrifuges and centrifugation protocols that can contribute to the diversity of the results [3]. In the present study, we used the 200g protocol for 12 minutes recommended by CHOUKROUN *et al.* (2006) [5], and used in the studies by GULSEN *et al.* (2017) [9]. However, some authors used 200G protocols for 10 minutes, or did not specify this information in the studies.

The pre and postoperative medication protocol has a direct influence on the evaluation of the variables in the present study. In the present study, dexamethasone was used in the preoperative period, which is proven to be a factor that contributes to the reduction of postoperative edema [11]. In addition, the association of an NSAID with a peripheral action analgesic in the postoperative period contributed to the low incidence and intensity of postoperative pain [11]. It is not possible to establish direct comparison measures between studies due to the diversity of drug protocols used.

Regarding the postoperative edema, GÜLŞEN (2017) [10] and Asutay *et al.* (2017) [11] presented results similar to the present study, with no reduction in

edema with the use of L-PRF in this type of surgery. The present study showed a statistically significant result only in relation to edema on the second postoperative day. Despite the statistically significant difference, when we look at the values, we find that the average difference between the test and control groups was 1 to 2 mm, which would not be clinically significant, Ozgul *et al* (2015) [13] observed that the use of L-PRF represented a slight improvement in the reduction of postoperative trismus, which is not in accordance with the results obtained in the present study. In his methodology, he performed the procedures on different patients. In the present study, we opted to perform the procedures on the same patient, which reduces the bias of individual variations in the inflammatory response. The use of L-PRF had no effect on the amount of mouth opening in the postoperative period of 2 and 7 days.

Kumar *et al* (2015) [14], Singh *et al* (2012) [15] and Zahid *et al* (2019) observed a statistically significant improvement in the pain of patients after the use of L-PRF, but Iqbal *et al* (2023) [17] observed statistically significant improvement in the pain just in the second day. While Ozgul *et al* (2015) [13], GÜLŞEN (2017) [8], Asutay *et al* (2017) [12] and Iqbal *et al.* (2023) [17] did not observe a reduction in postoperative pain in patients who received L-PRF. All studies used the visual analog scale as a method of choosing pain assessment. They have a similar methodology that used in the present study. These results indicate that L-PRF can improve pain in the first days, but the outcome with and without L-PRF seems to be the same.

The perception of patients regarding the benefits of L-PRF in the postoperative period was evaluated since it was not possible to establish the blindness of patients in this type of study since venipuncture and blood collection was necessary for use in only one of the extracted teeth. Thus, the authors decided to verify whether this finding could positively impact patients' responses regarding postoperative pain. Most patients reported that the side that received L-PRF had a better recovery and would perform the venipuncture again (57.14%). However, this effect seemed balanced, since six patients reported worse recovery and would not like to perform any surgical procedure again using venipuncture and blood collection. Methods that involve blinding can help to minimize this effect, however, they face the bioethical issue. It is important to emphasize that this procedure can be tolerated, is safe and little invasive, however, it is unpleasant for most patients, as it involves the use of a needle catheter.

The use of anti-inflammatory medication in the pre and postoperative period may have contributed to minimize the incidence of pain, edema and trismus in the present study. The reduced surgical time associated with less complex cases according to the Pell and Gregory classification are factors that also contribute to these results. Studies with standardized cases regarding the position and classification of wisdom teeth can clarify whether the PRF has benefits in more complex cases.

The present study has limitations regarding the small sample size, absence of blinding of patients and surgeons regarding the test and control side. In addition, despite having similar classifications, the levels of difficulty in removing third molars may have varied between the test and control sides, but all the procedures took similar duration. Three patients presented divergences in the classification between the test and control sides. The design of the split mouth study helps to reduce the variability of the inflammatory response and medications among individuals.

CONCLUSION

The use of L-PRF in impacted lower third molar surgeries did not present evident clinical benefits regarding maximum mouth opening and pain. However, the results in relation to edema were statistically significant in the postoperative period, demonstrating the reduction in edema. Most patients did not see benefits from this therapy and would not undergo venipuncture again.

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CONFLICT OF INTEREST STATEMENT

None declared.

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